gastrointestinal disorders

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*Brief Report*

# Elevated Plasma Adrenomedullin Levels in Patients with Unresectable Advanced Gastrointestinal Cancers

**Yoshinori Ozono [1,†], Hotaka Tamura [1,†], Kazuo Kitamura [2], Ayumu Hosokawa [3], Yukiko Otsuki [1], Hiroshi Hatada [1], Naomi Uchiyama [1], Satoshi Shimamoto [4], Koji Igarashi [4] and Hiroshi Kawakami [1,*]**

1 Division of Gastroenterology and Hepatology, Department of Internal Medicine, Faculty of Medicine, University of Miyazaki, Miyazaki 889-1692, Japan; yoshinori_ohzono@med.miyazaki-u.ac.jp (Y.O.); hotaka_tamura@med.miyazaki-u.ac.jp (H.T.); yukiko_ootsuki@med.miyazaki-u.ac.jp (Y.O.); hiroshi_hatada@med.miyazaki-u.ac.jp (H.H.); naomi_uchiyama@med.miyazaki-u.ac.jp (N.U.)
2 Frontier Science Research Center, University of Miyazaki, Miyazaki 889-1692, Japan; kazuokit@med.miyazaki-u.ac.jp
3 Department of Clinical Oncology, University of Miyazaki Hospital, Miyazaki 889-1692, Japan; ayhosoka@med.miyazaki-u.ac.jp
4 Bioscience Division, Reagent Development TOSOH Corporation, Ayase 252-1123, Japan; satoshi-shimamoto-wv@tosoh.co.jp (S.S.); kouji-igarashi-hk@tosoh.co.jp (K.I.)
* Correspondence: hiropon@med.miyazaki-u.ac.jp; Tel.: +81-985859797; Fax: +81-985859802
† These authors contributed equally to this work.

## Abstract

Background/Objectives: Adrenomedullin (AM) is a circulating peptide involved in tumor progression, angiogenesis, and fibrosis. However, its clinical utility as a biomarker in gastrointestinal cancers remains unclear. Methods: This single-center prospective observational study included patients with unresectable advanced gastrointestinal cancers (esophageal, gastric, colorectal, biliary tract, and pancreatic cancers) and healthy volunteers. Plasma AM levels were measured before the initiation of systemic chemotherapy in patients with cancer and at the time of enrollment in healthy volunteers. Results: In the unadjusted analyses, plasma mature and total AM levels were significantly higher in the cancer group than in healthy volunteers. Age was significantly associated with both mature and total AM levels, whereas sex did not show a significant association. After adjustment for age, between-group differences in mature and total AM levels were not statistically significant. Among patients with pancreatic cancer, plasma mature and total AM levels were significantly higher in stage IV than in stage III disease. Conclusions: Higher plasma AM levels were observed in the cancer group than in healthy controls in the unadjusted analyses; however, these differences were not statistically significant after adjustment for age. A stage-related difference was observed in pancreatic cancer. These findings should be considered hypothesis-generating and require validation in larger studies with appropriately matched control groups.

**Keywords:** adrenomedullin; gastrointestinal cancers; biomarker; pancreatic cancer



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## 1. Introduction

Adrenomedullin (AM) is a 52-amino acid peptide, widely expressed throughout the body [1]. AM exhibits vasodilatory, anti-inflammatory, and tissue-protective effects, and circulating AM levels increase in cardiovascular, renal, and inflammatory diseases [2–6]. In cancer biology, AM has been shown to promote tumor progression by stimulating tumor cell proliferation, inhibiting apoptosis, and enhancing angiogenesis and

lymphangiogenesis [7,8]. AM is overexpressed in several malignancies including pancreatic and prostate cancers, where it contributes to tumor growth [9–12]. In addition, elevated plasma AM levels have been reported in patients with pancreatic, breast, colorectal, and lung cancers [7,8].

Despite these findings, the clinical significance of circulating AM levels in patients with gastrointestinal cancers remains unclear. In particular, it is unknown whether plasma AM levels can be used as a biomarker for disease status or for supporting clinical management in patients with unresectable advanced gastrointestinal cancers.

We hypothesized that plasma AM levels might be elevated in patients with unresectable advanced gastrointestinal cancers compared with healthy individuals. Therefore, the aim of this study was to compare plasma AM levels between patients with unresectable advanced gastrointestinal cancers and healthy volunteers and to evaluate the potential of AM as a clinical biomarker.

## 2. Results

### *2.1. Participant Characteristics*

A total of 49 patients with unresectable advanced gastrointestinal cancers and 20 healthy controls were included in the study. The median age of the control group was 45 years (range, 20–73 years), and 5 (25%) participants were male. In contrast, the median age of the cancer group was 70 years (range, 44–82 years), and 32 (65%) patients were male. Significant between-group differences were observed in age and sex (both $p < 0.01$). The cancer group comprised 13 patients with esophageal cancer, 3 with gastric cancer, 9 with colorectal cancer, 9 with biliary tract cancer, and 15 with pancreatic cancer.

### *2.2. Plasma AM Levels in the Cancer and Control Groups*

In the unadjusted analyses, plasma mature and total AM levels were significantly higher in the overall cancer cohort than in the control group. In exploratory unadjusted cancer-type-specific comparisons, plasma mature and total AM levels were also significantly higher in each cancer-type subgroup than in the control group (Figure 1). Age was significantly associated with both mature and total AM levels, whereas sex was not significantly associated. After adjustment for age, differences in mature and total AM levels between cancer and control groups were no longer statistically significant.

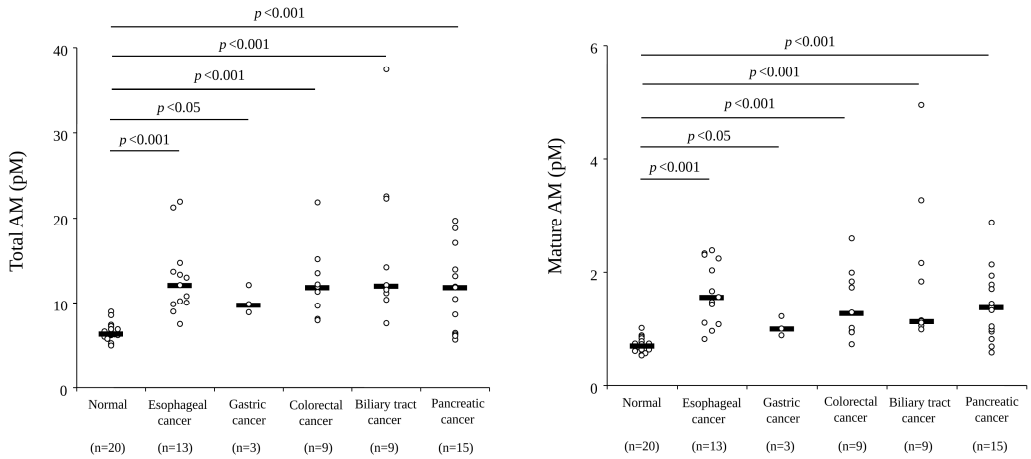


**Figure 1.** Unadjusted plasma mature and total AM levels in healthy controls and patients with unresectable advanced gastrointestinal cancers, stratified by cancer type. AM, adrenomedullin. Circles indicate individual values, and horizontal bars indicate medians.

### *2.3. Exploratory Stage-Stratified Analyses*

The stage-stratified analyses were exploratory. For esophageal cancer, no statistically significant differences between stage III/IVA and stage IVB disease were observed in plasma mature or total AM levels. Likewise, no statistically significant differences between stages III and IV in either colorectal or biliary tract cancer were observed. In pancreatic cancer, plasma mature and total AM levels were significantly higher in patients with stage IV disease than in those with stage III disease (Figure 2). Because only three patients had gastric cancer, no stage-stratified analysis was performed for this subgroup.

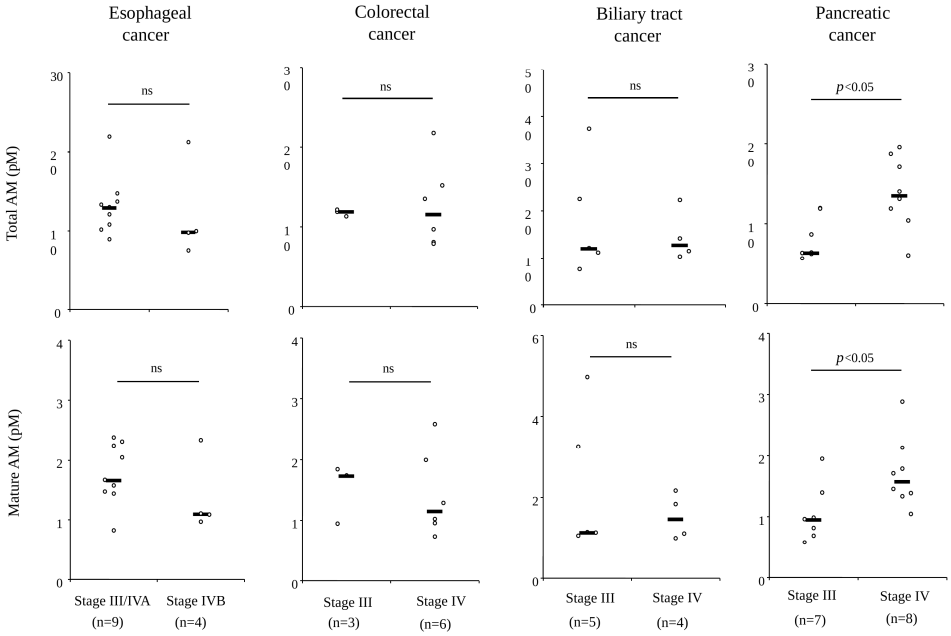


**Figure 2.** Plasma levels of mature and total AM in patients with unresectable advanced esophageal, colorectal, biliary tract, and pancreatic cancers by tumor staging. AM, adrenomedullin; ns, non-significant. Circles indicate individual values, and horizontal bars indicate medians.

## 3. Discussion

This study evaluated plasma AM levels in a cohort of patients with unresectable advanced esophageal, gastric, colorectal, biliary tract, and pancreatic cancers. In the unadjusted analyses, plasma mature and total AM levels were higher in the cancer group than in healthy controls; however, these between-group differences were not statistically significant after adjustment for age. In the exploratory stage-stratified analyses, a significant difference in plasma AM levels between stages III and IV was observed only in pancreatic cancer. No statistically significant stage-related differences were detected in esophageal, colorectal, or biliary tract cancers. These findings should be interpreted with caution because the subgroup sample sizes were small and the analyses could be underpowered. The gastric cancer subgroup included only three patients and was therefore too small for meaningful stage-stratified interpretation.

AM expression is elevated in various cancer tissues [9–12], and its plasma levels are increased in some patients with cancer [7,8]; however, the clinical utility of AM in cancer remains unclear.

In vitro studies have shown that AM affects the invasiveness of pancreatic cancer cells in a concentration-dependent manner [9]. These experimental findings provide a biological rationale for investigating the relationship between circulating AM and disease burden in pancreatic cancer; however, the present clinical data do not establish a causal relationship between AM and metastatic progression. Since invasion is a key component of metastasis,

it is important to recognize that AM is not only a circulating peptide of potential biomarker interest but also a biologically active peptide involved in tumor progression.

Unresectable advanced gastrointestinal cancers have poor prognosis. Further, reliable circulating biomarkers that can be repeatedly measured to indicate disease status or treatment response are limited. Recent advances in therapeutic approaches including nucleic acid-based therapeutics and emerging cell-based immunotherapeutic strategies highlight the need for biomarkers that can support longitudinal assessment during treatment [13,14]. Therefore, to clarify the clinical utility of AM and address the limitations of the present exploratory study, we are conducting a larger prospective study with an increased sample size and a control group with more comparable age and sex distributions. Plasma AM levels are being measured longitudinally during systemic chemotherapy to investigate whether tumor shrinkage is accompanied by a decrease in AM levels and whether disease progression is associated with an increase in AM levels. We are also comparing longitudinal changes in AM and conventional tumor markers such as CA19-9 and CEA, to characterize the potential advantages and limitations of AM as a circulating biomarker and to determine whether it may provide complementary information for assessing treatment response and disease status. Enrollment is expected to be completed by the end of 2028, with the primary analysis planned for 2029 after completion of a predefined follow-up period.

The present study is preliminary and hypothesis-generating, and has several limitations. First, significant differences in age and sex were observed between the cancer and control groups. Using ANCOVA, differences in mature and total AM levels between cancer and control groups were no longer statistically significant after adjustment for age. Therefore, higher AM levels observed in the unadjusted analysis could have been partly attributable to older age of the cancer group. Further, independent associations between cancer status and plasma AM levels cannot be established from the present data. Second, the total sample size was small, and the subgroups for each cancer type were even smaller, particularly the gastric cancer subgroup ($n = 3$). Therefore, an absence of statistically significant stage-related differences in esophageal, colorectal, and biliary tract cancers may be due to an underpowered study and should not be interpreted as evidence of lack of associations. Third, the cancer-type subgroups were small, and hence, it cannot be concluded that AM is a general biomarker across gastrointestinal cancers. These limitations are being addressed in our ongoing larger prospective study using an increased sample size and a control group with more comparable age and sex distributions.

## 4. Materials and Methods

### *4.1. Study Design*

This single-center, prospective, observational study was conducted at the University of Miyazaki Hospital. We prospectively enrolled treatment-naive patients with unresectable advanced gastrointestinal cancers (esophageal, gastric, colorectal, biliary tract, and pancreatic cancers) and healthy volunteers as controls. Eligible participants were patients with cancer or healthy volunteers aged 18 years or older at the time of informed consent. Patients with early-stage cancer who were not candidates for systemic chemotherapy were excluded. Participants were also excluded if they had conditions that might affect plasma AM levels including hypertension (systolic blood pressure $\geq$ 140 mmHg or diastolic blood pressure $\geq$ 90 mmHg), current use of antihypertensive medication [4,5], serum creatinine greater than 1.5 mg/dL [4], acute heart failure, or sepsis [2,3,6]. Peripheral blood was collected prior to systemic chemotherapy for each cancer patient and at enrollment for controls. Plasma levels of mature AM and total AM were measured using commercially available automated immunoassay systems (AIA-System; Tosoh Corporation, Tokyo, Japan), as described previously [15]. Mature AM is the physiologically active form of the peptide. In

contrast, total AM represents the sum of intermediate (glycine-extended) AM and mature AM. The assays were performed by an experienced technician who was blinded to all other clinical data analyzed in the present study.

### *4.2. Statistical Analysis*

Statistical analyses were performed using the EZR ver. 4.2.2 (Saitama Medical Center, Jichi Medical University, Saitama, Japan). Plasma AM levels and age are expressed as medians. Continuous variables were compared using the Mann–Whitney U test, and categorical variables were compared using Fisher's exact test. To assess potential confounding by age and sex, their associations with plasma AM levels were evaluated using ANCOVA. An age-adjusted ANCOVA was then performed as a sensitivity analysis to compare plasma AM levels between the cancer and control groups. $p$ values $< 0.05$ were considered statistically significant.

**Author Contributions:** Y.O. (Yoshinori Ozono) and H.T. developed the study protocol, drafted the manuscript, and performed the statistical analyses. K.K. conceived the study. A.H., Y.O. (Yukiko Otsuki), H.H. and N.U. acquired the data. S.S. and K.I. reviewed the literature and contributed to data interpretation. H.K. conceived and supervised the study, developed the study protocol, and critically revised the manuscript. All authors have read and agreed to the published version of the manuscript.

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**Institutional Review Board Statement:** This study protocol was reviewed and approved by the Research Ethics Committee, Faculty of Medicine, University of Miyazaki, approval number [O-1011]. All procedures were conducted in accordance with the principles of the Declaration of Helsinki.

**Informed Consent Statement:** Written informed consent was obtained from all participants prior to enrollment in the study.

**Data Availability Statement:** The data that support the findings of this study are available from the corresponding author upon reasonable request. The data are not publicly available because they contain information that could compromise the privacy of the research participants.

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**Conflicts of Interest:** S.S. and K.I. are employees of Tosoh Corporation. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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